AMENDMENT TO SPECIFICATION

From page 1, line 19 to page 2, line 2, amend as follows:

Biological organisms generate harmful reactive oxygen species (ROS) and various free radicals in the course of normal metabolic activities of tissues such as brain, heart, lung, and muscle tissue (Halliwell, B. and Gutteridge, J.M.C., eds. ~~Free Radicals in Biology and Medicine~~[Free Radicals in Biology and Medicine], (Oxford: Clarendon Press, 1989)). The most reactive and, therefore, toxic ROS and free radicals include the superoxide anion ($O_2\cdot^-$), singlet oxygen, hydrogen peroxide (H_2O_2), lipid peroxides, peroxinitrite, and hydroxyl radicals. Even a relatively small elevation in ROS or free radical levels in a cell can be damaging. Likewise, a release or increase of ROS or free radicals in extracellular fluid can jeopardize the surrounding tissue and result in tissue destruction and necrosis. Indeed, hydrogen peroxide, which is somewhat less reactive than the superoxide anion, is a well known, broad spectrum, antiseptic compound. In eukaryotes, a major source of superoxide anion is the electron transport system during respiration in the mitochondria. The majority of the superoxide anion is generated at the two main sites of accumulation of reducing equivalents, i.e., the ubiquinone-mediated and the NADH dehydrogenase-mediated steps in the electron transport mechanism. Hydrogen peroxide is generated metabolically in the endoplasmic reticulum, in metal-catalyzed oxidations in peroxisomes, in oxidative phosphorylation in mitochondria, and in the cytosolic oxidation of xanthine (see, for example, Somani et al., "Response of Antioxidant System to Physical and Chemical Stress," *In* ~~Oxidants, Antioxidants, and Free Radicals~~[Oxidants, Antioxidants, and Free Radicals], chapter 6, pp. 125-141, Baskin, S.I. and H. Salem, eds. (Taylor & Francis, Washington, D.C., 1997)).

From page 13, line 32 to page 14, line 13, amend as follows:

"Free radical", as understood and used herein, refers to any atom or any molecule or compound that possesses an odd (unpaired) electron. By this definition, the superoxide anion is also considered a negatively charged free radical. The free radicals of particular interest to this invention are highly reactive, highly oxidative molecules that are formed or generated during normal metabolism, in a diseased state, or during treatment with chemotherapeutic drugs. Such

free radicals are highly reactive and capable of causing oxidative damage to molecules, cells and tissues. One of the most common and potentially destructive types of the free radicals other than the superoxide anion is a hydroxyl radical. Typically, the generation of ROS, such as superoxide anion or singlet oxygen, also leads to one or more other harmful free radicals as well. Accordingly, phrases such as "ROS and free radicals" or "ROS and other free radicals", as understood and used herein, are meant to encompass any or all of the entire population of highly reactive, oxidative molecular species or compounds that may be generated in a particular metabolic state or condition of cells and tissues of interest (see, for example, Somani et al, "Response of Antioxidant System To Physical and Chemical Stress," *In* ~~Oxidants, Antioxidants, and Free Radicals~~[Oxidants, Antioxidants, and Free Radicals], chapter 6: 125-141 (Taylor & Francis, Washington, D.C., 1997)).

From page 21 line 3 to line 21, amend as follows:

The peptide compounds can be made using standard methods or obtained from a commercial source. Direct synthesis of the peptides of the peptide compounds of the invention may be accomplished using conventional techniques, including solid-phase peptide synthesis, solution-phase synthesis, etc. Peptides may also be synthesized using various recombinant nucleic acid technologies, however, given their relatively small size and the state of direct peptide synthesis technology, a direct synthesis is preferred and solid-phase synthesis is most preferred. In solid-phase synthesis, for example, a suitably protected amino acid residue is attached through its carboxyl group to a derivatized, insoluble polymeric support, such as cross-linked polystyrene or polyamide resin. "Suitably protected" refers to the presence of protecting groups on both the α-amino group of the amino acid, and on any side chain functional groups. Side chain protecting groups are generally stable to the solvents, reagents, and reaction conditions used throughout the synthesis and are removable under conditions, which do not affect the final peptide product. Stepwise synthesis of the polypeptide is carried out by the removal of the N-protecting group from the initial (i.e., carboxy terminal) amino acid, and coupling thereto of the carboxyl end of the next amino acid in the sequence of the polypeptide. This amino acid is also suitably protected. The carboxyl group of the incoming amino acid can be activated to react with the N-terminus of the bound amino acid by formation into a reactive group such as formation into a carbodiimide, a symmetric acid anhydride, or an "active ester"

group such as hydroxybenzotriazole or pentafluorophenyl esters. The preferred solid-phase peptide synthesis methods include the BOC method, which utilizes tert-butyloxycarbonyl as the α-amino protecting group, and the FMOC method, which utilizes 9-fluorenylmethloxycarbonyl to protect the α-amino of the amino acid residues, both methods of which are well-known by those of skill in the art (see, Stewart et al., Solid-Phase Peptide Synthesis (W. H. Freeman Co., San Francisco 1989); Merrifield, *J. Am. Chem. Soc.*, 85:2149-2154 (1963); Bodanszky and Bodanszky, ~~The Practice of Peptide Synthesis~~[The Practice of Peptide Synthesis] (Springer-Verlag, New York 1984), incorporated herein by reference).

From page 32 line 4 to line 12, amend as follows:

One of the most dangerous side effects of a drug has been reported for the neuroleptic, clozapine, which was the first drug with major potential as an anti-schizophrenic therapeutic activity (see, Somani et al., ~~Oxidants, Antioxidants, and Free Radicals~~[Oxidants, Antioxidants, and Free Radicals] (S.I. Baskin And H. Salem, eds.) (Taylor And Francis, Washington D.C., 1997), pages 125-136). Approximately 1-2% of clozapine-treated patients develop agranulocytosis, which is correlated with the production of ROS (Fischer et. al., *Molecular Pharm.*, 40:846-853, 1991). According to the invention, a peptide compound as described herein is administered to clozapine-treated patients to upregulate the SOD and/or CAT, which counteracts the undesirable and harmful increase in ROS and other free radicals and, thereby, reduces the risk of developing agranulocytosis.

From page 36 line 9 to line 21, amend as follows:

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, ~~Tween 80~~[TWEEN 80] (polysorbate 80)) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be

employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as those described in *Pharmacoplia Halselica.*

From page 38 line 27 to line 30, amend as follows:

Details concerning dosages, dosage forms, modes of administration, composition and the like are further discussed in a standard pharmaceutical text, such as ~~Remington's Pharmaceutical Sciences~~ [Remington's Pharmaceutical Sciences], 18th ed., Alfonso R. Gennaro, ed. (Mack Publishing Co., Easton, PA 1990), which is hereby incorporated by reference.

From page 44 line 26 to line 33, amend as follows:

The peptides were synthesized using standard procedures. Briefly, the peptides were synthesized using the solid phase Merrifield process (Merrifield, R. B., *J. Am. Chem. Soc.*, 85:2149-2154 (1963)). This method allows the synthesis of a peptide of a specific amino acid sequence bound on a polymeric resin. Each newly synthesized peptide was then released from the resin by treating with trifluoroacetic acid (TFA). The resultant trifluoroacetic acid peptide salt was purified by ether precipitation according to standard procedures (see, E. Groos and Meienhofer, *In* ~~The peptides, analysis, synthesis, biology, vol. 2~~[The peptides, analysis, synthesis, biology, vol. 2], (Academic Press, New York 1983)).

From page 45 line 21 to line 31, amend as follows:

The RT-PCR method (see, for example, Innis et al., ~~PCR Protocols: A Guide to Methods and Applications~~[PCR Protocols: A Guide to Methods and Applications], (Academic Press, San Diego, 1990)) was used to investigate the upregulation of the specific mRNA that codes for the enzyme superoxide dismutase (SOD).

Primary cortical cultures were obtained by growing newborn rat brain cortical cells in ~~Delbecco's~~[Dulbecco's] modified Eagle medium supplemented with 25 mg/ml of gentamycin and 10% fetal calf serum. The cells were isolated from the E-21 cortex of rat brain, plated at a density of 1 x 10^5 per ml and grown to confluence within four to five days in an atmosphere

containing air and 5% CO_2 at 37°C as described in Cornell-Bell et al., *Science, 247*: 470-473 (1990) and *Cell Calcium, 12*: 185-204 (1991). Cultures were grown in 20 ml flasks as a monolayer and then exposed to various concentrations of peptides for studies of the effects of peptides on upregulation of genes for SOD and CAT and on the transmigration of transcription factor AP-1 to cell nuclei.

From page 50 line 10 to line 27, amend as follows:

AP-1 transcription factor activation was assayed using an electrophoretic mobility shift assay (EMSA), as described by Adams et al., *J. Leukoc. Biol.*, 62:865-873 (1997)). Cultures of primary rat neurons (Cornell-Bell et al., *Cell Calcium, 12*: 185-204 (1991)) were stimulated for 3 hours with various concentrations (0, 1, 10, 100 ng/ml) of peptide CMX-9236. Nuclear extracts prepared as described above were separated by gel electophoresis on non-denaturing gels and subjected to the EMSA procedure. This EMSA used an AP-1 synthetic duplex probe (Angel, P., 1987, *Cell* 49:729-739) having the sequence 5'-CGCTTGATGACTCAGCCGGAA (SEQ ID NO:33) and its antisense copy (complement strand), which were end-labeled with P^{32} using polynucleotide kinase and (γ-P^{32})-ATP. For the EMSA reaction, the labeled probe (0.5 pmol) was mixed with 3 μg of nuclear extract protein in a solution containing 10 mM Tris-HCl, pH 7.5, 50 mM NaCl, 1 mM EDTA, 1 mM dithiothreitol, 5% glycerol, 0.02% β-mercaptoethanol, and 1 μg of poly-dI/dC (~~Pharmacia~~[PHARMACIA]). Reaction mixtures were incubated at 25°C for 20 minutes to allow complete complex formation by the duplex with its appropriate AP-1 protein. The mixture was then electrophoresed under non-denaturing conditions through 4% polyacrylamide gels in 0.5X TBE buffer (45 mM Trisma base, 45 mM boric acid, 1 mM EDTA). The gels were dried on 3 mm paper. Bands were visualized by autoradiography at -80°C with one intensifying screen and quantified by laser densitometry. The upregulation of AP-1 and the activation and upregulation process of AP-1 was compared to control cultures.

From page 59 line 8 to line 24, amend as follows:

Five grams of the raw GVA dry powder from ~~Qeva, Inc.~~[QEVA, INC.] (Calgary, Ontario, Canada), were extracted with 100 ml of water at room temperature for 30 minutes. The water soluble components ("GVAW") were then separated from the insoluble residue by centrifugation for 30 minutes at 5,000 x *g*. The residue was further extracted by re-suspension in

50 ml of water and stirring for additional 30 minutes. The mixture was then re-centrifuged (30 minutes at 5,000 x *g*) and the supernatants from the two extracts were combined to give a crude yellow extract. This was re-centrifuged at 10,000 x *g* for 30 minutes at room temperature. The supernatant fraction was removed and sterilized by filtration through a Millipore filter (0.2 µm pore size) to give a clear yellow solution. This clear yellow solution was then concentrated to 10-20 ml in a rotary evaporator at 30°C under mild vacuum, and lyophilized to give the fraction GVAW as a brown, fluffy powder (yield 15-20%). This fraction contains an active peptide that can up-regulate SOD (see Table 5) in primary rat brain cortical cultures as described above.

Additional purification of the GVAW fraction was carried out by column chromatography using Biogel (PD-10) from ~~Bio-Rad Laboratories~~[BIO-RAD LABORATORIES, INC.] (Hercules, CA 94547). This separated the peptides with a molecular weight (MW) higher than 6,000 daltons from those with a MW of less than 6,000 daltons to give two fractions: GVA +6 and GVA –6, respectively, and to give yields (based on raw material) of lyophilized products of 8-10% and 3-6%, respectively.